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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Kendall A. Smith Confirmation No.: 2206

Application No.: 09/708,635 Art Unit: 1648

Filed: September 22, 2000 Examiner: J. Parkin

For: Low Dose IL-2 For Potentiation of Immunity

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION OF KENDALL A. SMITH

I, Kendall A. Smith, M.D., do hereby declare and state as follows:

1. I am a citizen of the United States and more than 21 years of age. I received a M.D. *summa cum laude* from the Ohio State University in 1968. I am certified by the American Board of Internal Medicine. I am currently a Professor of Medicine at Weill Medical College and a Professor of Immunology at Weill Graduate School of Medical Sciences, both of Cornell University. My Curriculum Vitae is attached to this declaration.

2. I am the inventor of the subject matter described and claimed in the above-identified patent application.

3. The trials described below were conducted under my direction. The data set forth in Figures 1-4 set forth the results of these trials.

4. CD4+ and CD8+ T cell and Natural Killer cell concentrations were monitored for HIV+ patients who initially received, and subsequently discontinued antiviral therapy. The study consisted of three steps, each step consisting of about 12 weeks. Antiviral therapy was discontinued at week 12 (conclusion of step I). Circulating cell measurements were reported (% of Baseline) relative to levels at the beginning of the study (t = 0 weeks). One group of 11 subjects received one subcutaneous injection of low dose IL-2 daily (about 1,200,000 IU/m^2 body surface) throughout the three steps, and one group of 17 subjects did not receive IL-2 at any time.

5. Patients in both IL-2 and non-IL-2 groups were randomly placed in two subgroups, one subgroup receiving an HIV vaccine during the first twelve weeks (during step 1), and one subgroup receiving a placebo vaccine. The two subgroups in Figures 1-3 are plotted together, i.e. data is shown for the IL-2 group and the non-IL-2 group. I do not believe that the HIV vaccine has any effect on the observed changes in lymphocyte concentrations of the group that received IL2 vs. the group that did not receive IL2. Nevertheless, any effects due to the HIV vaccine will be averaged out due to the HIV vaccine subgroup being included in both the IL-2 group and non-IL-2 group.

6. Steps II and III demonstrate the two group's immune response after discontinuation of anti-viral treatment. To remain eligible for step III, plasma HIV concentrations must be below 30,000 molecules/mL and CD4+ cell concentrations must be above 250.

7. Figure 1 demonstrates the CD4 + T cell % baseline for the three step study period. The CD4 + T cell concentrations for the IL-2 group were generally at or above baseline after discontinuation of antiviral therapy (steps 2 and 3), while the CD4 + T cell concentrations generally fell below baseline for steps 2 and 3 in the non IL-2 group.

8. Figure 2 demonstrates the CD8 + T cell % baseline for the three step study period. The CD8 + T cell concentrations for the IL-2 group were generally above baseline after discontinuation of antiviral therapy (steps 2 and 3), and were about 2-fold greater than the CD8 + T cell concentrations observed in the non-IL-2 group.

9. Figure 3 demonstrates the Natural Killer cell % baseline for the three step study period. The Natural Killer cell concentrations for the IL-2 group were generally above baseline after discontinuation of antiviral therapy (steps 2 and 3), while the Natural Killer cell concentrations for the non-IL-2 group generally remained at baseline.

10. Figure 4 demonstrates plasma HIV concentrations (molecules per ml) for the three step study period. During step 1, i.e. while both groups received antiviral treatment,

the HIV concentrations were at or below the lower limit of detection (about 50 molecules per ml). After the discontinuation of the antivirals (steps II and III) HIV became detectable for all subjects. These data show that CD4 +, CD8 +, Natural Killer cell concentrations were not affected by the detectable HIV viral loads shown by patients after discontinuation of antiviral therapy, when these patients are administered low dose IL-2, according to the present invention.

11. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the instant application or any patent issued thereupon.

Date 12/15/04

Kendall A. Smith, M.D.